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EPIDEMIOLOGICAL STUDIES OF CANCER FREQUENCY AND CERTAIN ORGANIC CONSTITUENTS OF DRINKING WATER--A REVIEW OF RECENT LITERATURE PUBLISHED AND UNPUBLISHED

prepared for the

Environmental Protection Agency

Office of Drinking Water
Criteria and Standards Division

by the

Epidemiology Subcommittee
of the
Safe Drinking Water Committee

Board on Toxicology and Environmental Health Hazards
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16. ABSTRACT

The epidemiological studies (published and unpublished) which comprise the sum total of epidemiological work on the subject of trihalomethanes in drinking water, were reviewed by the subcommittee. The subcommittee summarized the various studies, made a critical assessment, pointed out where it believes the evidence is deficient, and discussed the potential for further research on this subject. The probabilities of false associations when many comparisons are made were also considered when final conclusions were made.

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EPIDEMIOLOGICAL STUDIES OF CANCER FREQUENCY AND CERTAIN ORGANIC CONSTITUENTS OF DRINKING WATER-- A REVIEW OF RECENT LITERATURE, PUBLISHED AND UNPUBLISHED

After comparing cancer rates among people in Louisiana whose drinking water comes from the Mississippi River with rates in populations served with water from other sources, Harris (1974) concluded that something in the river water led to increased cancer rates. He suggested that the lower Mississippi contained many chemical pollutants, some, or some combination of which were carcinogenic.

The initial study was challenged by DeRouen and Diem (1975a, 1977) and several other hypotheses put forth. At that time the Environmental Protection Agency (EPA) was monitoring a large number of chemicals in U.S. water suplies--among them chloroform and the other trihalomethanes (THM's). The National Cancer Institute (NCI) was also studying the biological effects of chloroform in its large animal bioassay program and subsequently demonstrated an increase in liver and kidney tumors among animals exposed to high doses of chloroform (Page and Saffioti 1976).

Given these several pieces of information, the EPA asked a number of research groups to determine whether there was indeed a relationship between cancer rates and chloroform and other THM's in water supplies. Even though the liver and kidney were the only sites at increased risk in the animal experiments, the various research groups attempted to

evaluate the cancer risk at many other sites as well. The rationale for this is that exposure to a single carcinogen may result in cancer at different sites in different experimental animals and in humans. For example, vinyl chloride has produced nephroblastoma in rats but not in humans. There is also ample evidence of chemicals which produce cancer in some specieis but not in others, for example, 2 napthylamine is a potent bladder carcinogen in humans, dogs, and monkeys, but is inactive in rats and mice.

Most of the EPA requested studies used indirect evidence of the presence of THM in water supplies. Populations receiving surface water, which often contains organic materials and is sometimes treated with chlorine, were contrasted with those receiving ground water. Because ground water usually contains less organic matter and is less often chlorinated in the purification process than surface water, it is less likely to contain THM's. Authors of two studies used direct measurements of chloroform and other THM concentrations, which had been obtained by the EPA in two recent analytical surveys in a regression equation for U.S. county mortality rates with allowance being made for various demographic factors by including further linear regression terms.

The above epidemiological studies (published and unpublished), which comprise to our knowledge the sum total of epidemiological work on this subject, were reviewed by the subcommittee. None of the studies reviewed were able to

adequately take into account many well established risk factors for cancer rates at different sites. For example, for bladder cancer one needs to control for occupation, cigarette smoking, use of alcohol and drugs, nonaqueous sources of THM, coffee consumption, socioeconomic status and ethnicity. The studies also had to assume that present exposures to THM reflected lifetime exposures of the populations studied: this is not only because THM concentrations in water have only recently been measurable, but also because the necessary information on migration patterns with associated THM concentrations is not readily available.

The subcommittee has summarized the various studies, made a critical assessment, pointed out where it believes the evidence is deficient, and discussed the potential for further research on this subject. The probabilities of false associations when many comparisons are made were also considered when final conclusions were made.

SUMMARY AND CONCLUSIONS

The studies that the subcommittee reviewed were divided into two groups: those in which nonspecific measures of exposure to putative carcinogens in water (e.g., the use of surface water vs. ground water) were examined and those in which water quality was characterized by measurements of THM concentrations. The subcommittee gave greater weight to the conclusions of the latter group of studies because crude

measures of exposure, which lead to comparisons of cancer between surface water users and ground water users, must be of limited value. They do not permit the quantitation of exposure to contaminants in water consumed, which is needed to determine dose-response relationships between THM concentrations and cancer frequencies and to estimate the effects of reducing THM concentrations.

The conclusions drawn in the second group of studies, in which many cancer sites were examined, suggest that higher concentrations of THM's in drinking water may be associated with an increased frequency of cancer of the bladder. The results do not establish causality, and the quantitative estimates of increased or decreased risk are extremely crude. The effects of certain potentially important confounding factors, such as cigarette smoking, have not been determined.

The bladder is not one of the sites found at increased risk in experiments on animals exposed to chloroform. Tumors of the liver and kidney developed in laboratory animals.

The positive association found for bladder cancer was small and had a large margin of error; not only statistical, but much more importantly because of the very nature of the studies. Hogan et al. (1978, unpublished) found regression coefficients of bladder cancer mortality (deaths per 10^5 per year) on chloroform concentration (μg/l) in drinking water to be approximately 0.003 for males and 0.0021 for females.

Thus, if there is a causal relationship, an increase in chloroform concentration of 100 μg/l might lead to increases of 0.3 deaths per 10^5 per year from bladder cancer in males and 0.2 deaths per 10^5 per year in females. These compare with the U.S. National Mortality Rates (1950-1969) for cancer of the bladder of 6.8 in males and 2.4 in females. Thus, a decrease of 100 μg/l of chloroform in water may lead to a 4.4% decrease in bladder cancer death rates in males and 6.7% in females.

These changes which have been shown in case-control studies to be explicable by as little as 1 to 2 cigarettes per day differences in average cigarette consumption, would probably be too small to be distinguished from possible confounding effects by any epidemiological study. Situations that could be more favorable for investigation should be sought so that further epidemiological work might be more rewarding.

STUDIES BASED ON INDIRECT MEASURES OF WATER QUALITY

Mississippi River-Louisiana, First Study

The first papers reporting relationships between cancer frequency and water quality were those of the Environmental Defense Fund (Harris 1974, unpublished; Page et al. 1976). These two papers were based on the published cancer motrality data by county in the United States (Mason and McKay 1974). The proportions of each Louisiana parish's water that was obtained from the Mississippi River were related, in a regression analysis, to cancer mortality. The study was controlled for urban-rural status, income, and employment in certain potentially hazardous industries. Significant positive correlation coefficients were found in two of the four race-sex groups for genitourinary cancer, and in all four groups for gastrointestinal cancer.

Mississippi River-Louisiana, Second Study

Using the same water quality data and county mortality data as Harris (1974, unpublished), DeRouen and Diem (1975b, unpublished) reported a major difference between northern and southern regions of Louisiana--a potentially important confounding factor for the cancer-water association. This was also noted by Buncher (1975, unpublished). DeRouen and Diem's analyses of cancer mortality and water source were restricted to southern Louisiana where parishes using only Mississippi River water were located. DeRouen and Diem

compared cancer mortality at 16 anatomic sites in four race-sex groups (52 site-sex-race groups in all) between persons receiving river water and those who did not. They found seven positive associations ($P<.05$) of mortality with use of river water in one or more sex-race groups for seven sites or site groups. Similarly, significant negative associations were found for seven sites. The consistency of associations in both sex and racial groups suggested positive associations for cancer of the bladder, breast, rectum, and large intestine, and negative associations (i.e., lower mortality in populations using river water) for cancer of the liver and corpus uteri. Cancer of the lung and cervix uteri had a significant positive association in one population and a significant negative association in another.

Ohio River Area, First Study

A similar approach was used on data from the Ohio River area. Buncher (1975, unpublished) studied the four-state area comprised of Ohio, West Virginia, Kentucky, and Indiana; Kuzma et al. (1977) confined their attention to Ohio. In the Ohio study, white males and females in all Ohio counties were compared according to the predominance of surface or ground water in their supplies. Sites with statistically significant ($P<.05$) excess mortality associated with surface water were the stomach in males and females and the bladder in males. In two additional site-

sex groups, the liver and breast in females were positive at the 20% level. These rates were adjusted for age, county population, percent urbanization, median income, an index of manufacturing activity, and an index of agricultural, forestry, and fishing activity.

Ohio River Area, Second Study

Harris et al. (1977, unpublished) reviewed the Ohio studies. Although they generally agreed with the findings of Kuzma et al. (1977), they failed to confirm the positive association for liver and breast cancer in females. In addition, they reported positive associations for the esophagus in males (not studied by Kuzma) and the pancreas in males.

They studied the effect of water source on cancer mortality by regression analysis similar to that used in the first Ohio area study, but they used as a water variable the percentage of a county population that received surface water.

Upstate New York

Alavanja et al. (1977, unpublished) conducted a case-control study of persons dying with gastrcintestinal or genitourinary cancer in several counties in upstate New York. The study was first confined to women to decrease the potentially confounding factor of occupational exposures,

and the cancer sites were selected on the basis of indications from prior reports. Consequently, this may be thought of as an hypothesis-testing study. Each cancer case was individually matched with a woman dying of a cause other than cancer.

Matching variables were county, age, race, and birthplace. Statistical analysis procedures did not take the matching into account, but it is impossible to judge the effect of this omission. Water supplies were determined from addresses and were characterized as chlorinated or not chlorinated and as surface or ground water. A doubling of risk was found to be associated with chlorinated supplies in urban areas. A 50% increase in risk was found to be associated with chlorinated ground water when compared with nonchlorinated water in rural areas. There was no increase (risk ratio 1.01) in rural areas supplied with chlorinated surface water in comparison with rural areas using nonchlorinated water.

In 1978, Alavanja's study was expanded to include men. He reported that "Males living in the chlorinated water areas of Erie, Rensselaer and Schenectady counties and females living in the chlorinated water areas of Erie and Schenectady counties are at a greater risk of gastrointestinal and urinary tract cancer mortality than are individuals living in nonchlorinated water areas. Moreover, this excess risk of GI and UT cancer mortality is not due to a disparity in the age, race or ethnic distribution of the

population or to an urban/rural factor, or hazardous occupation, or to inorganic carcinogens (Cd, As, Be, Pb, Ni, No_3^-) or a surface/ground water difference." In one county (Chautauqua) there was a significant deficit of both kinds of cancer mortality in chlorinated areas.

Because of the large population of Erie County, the data acquired there strongly influences the total risks reported. Urbanization is a potentially confounding variable in the study of effects of chlorination, and parcelling out shares of the excess risk between urbanization and chlorination does not seem possible, although some attempts have been made. For example, urban and rural nonchlorinated areas were compared with urban and rural chlorinated areas.

Washington County, Maryland

Kruse (1977, unpublished) studied cancer of the kidney and liver in a population in Washington County, which includes the city of Hagerstown, Maryland. This population has been investigated extensively as an epidemiological community model, and the source of home drinking water had been determined in an earlier survey. This previously gathered information was used in a total population study designed to correlate water source, characterized as chlorinated or not chlorinated, with presence or absence of cancers at specific sites. The approach involved estimating the effect of water source through a multivariate analysis including eight additional potentially confounding

demographic and sociological variables. There was an increased incidence of liver cancer associated with the chlorinated water supply, with a risk ratio of 1.5, but the increase was not statistically significant at the 20% level. Similarly, a decrease in incidence of cancer of the kidney with chlorination (risk ratio, 0.96) was not significantly associated with water source. There were only 91 cancer cases in this study.

Los Angeles County

In Los Angeles County Mah et al. (1977, unpublished) correlated cancer mortality rates and incidence rates with chloroform content in drinking water. They divided the county into nine subareas categorized as having low, medium, or high chloroform content of the water. Eight cancer sites were studied: esophagus, stomach, colon, rectum, liver, lung, kidney, and bladder. Tabular and graphic inspection of data and limited analyses suggested no association of cancer rates with chloroform content of water, and the investigators believed no more detailed analysis was justified in view of certain limitations in the basic material, viz., absence of precise data on chloroform content, extensive use of bottled and other water transported from other sources by this population, and large population movements into and out of Los Angeles County in the last several decades.

Ohio River, Third Study

Salg (1977, unpublished) studied populations in areas served by water from the Ohio River, including all counties within the boundaries of the Ohio River Valley Basin as determined from water drainage maps. These counties lie within a seven-state area: Illinois, Indiana, Kentucky, Ohio, Pennsylvania, Tennessee, and West Virginia. The exposure variables, indicating possible intake of pollutants in the water supply, were the percent of county population served by surface water and the percent served by prechlorinated (defined as chlorination prior to filtration) water. The outcome variable was cancer mortality for 346 counties, specific for 19 anatomic sites of cancer. The main variables were investigated in a multivariate analysis using as possible confounding factors nine variables representing demographic and socioeconomic characteristics of the counties.

There were positive associations ($P<.2$) for 13 of the 19 site categories in one or more of four sex-race population groups. Similarly significant negative associations were found for seven site categories in one or more populations. In two or more population groups there were positive associations for cancer of the esophagus, rectum, breast, larynx, and for Hodgkin's disease.

Salg interpreted her findings to indicate the need for further study of carcinoma of the large intestine, rectum, and bladder. Large intestine cancers were found to be

significantly increased in white males. Bladder cancer incidence was significantly elevated in white males and significantly decreased in nonwhite females.

Pittsburgh Study

Carlson and Andelman (1977, unpublished) conducted a study in the Pittsburgh region. They associated site, race, and sex-specific, age-adjusted cancer incidence rates by 1969-1971 census tract with drinking water, which was characterized by source of raw water (surface, ground, and river) and by water treatment plant.

Their paper is principally an investigation of statistical methodology. Their general conclusion is that significant associations, both positive and negative, are found between water quality and cancer incidence. The data are not summarized in a way that permits identification of cancers of specific sites.

New Jersey Study

Vasilenko and Magno (1975, unpublished) studied all 21 counties in New Jersey to determine the relation between water source and age-adjusted cancer mortality from lung, stomach, and urinary tract cancer of white males between 1950 and 1969. Water quality was estimated from the ratio of the number of households served by public systems and private water companies to the number served by individual

wells. Confounding variables included in the analysis were urban-rural characteristics, income, education, migration, occupation, industrialization, and sulfur dioxide concentration in the air.

In a multiple regression analysis, the water variable was positively associated with mortality from respiratory cancer and stomach cancer. A nonsignificant negative association was found for bladder cancer.

SUMMARY

Nine of the ten studies described above showed a number of associations, some of which were statistically significant, between indirectly characterized water quality and cancer rates (incidence or mortality). One, the Los Angeles County study, reported no associations, but this study appeared to have greater limitations than any of the others.

Cancer rates at several sites were positively associated with water quality in one or another study, but no site consistently predominated. The bladder, stomach, large intestine, and rectum, which were cancer sites identified in a number of geographic areas, warrant further study.

The effects of certain important demographic variables were considered in a number of studies of this group, but other confounding factors, e.g., cigarette smoking, were not.

STUDIES BASED ON TRIHALOMETHANE CONCENTRATIONS

Three studies (Cantor et al. 1977, unpublished; Hogan et al. 1978, unpublished; and McCabe 1975, unpublished) have been conducted using measured THM concentrations. All three studies used cancer mortality rather than incidence data, although the latter are usually preferable. These studies could not however use incidence data as they are not generally available for the areas covered by the THM surveys.

Cantor et al. studied the relation between age-standardized cancer mortality for 1968 to 1971 of white men and women in U.S. counties that were categorized as urban on the basis that more than 50% of the county population lived in urban areas in 1970.

County THM concentrations were estimated from data obtained in two surveys conducted by the EPA (U.S. Environmental Protection Agency 1975). The National Organics Reconnaissance Survey (NORS) sampled finished water in 80 water treatment plants across the country, and a survey conducted by EPA's Region V office covered 83 plants in the states of Illinois, Indiana, Michigan, Minnesota, Ohio, and Wisconsin.

The analysis took into account the median school years completed by county inhabitants over age 25, foreign stock composition of county, county population, ratio of 1970 to 1950 county population, percent of county that is urban, percent of the county work force engaged in all

manufacturing industries (U.S. Census 1970), and major geographic region of the United States. An attempt was made by multivariate regression to explain the variability among counties of mortality rates for each site of cancer with sex-specific mortality rates greater than 1.5/100,000/yr. The residual mortality rates, which were "unexplained" by these other variables, were then correlated directly with measured THM levels (logarithms of the concentrations) for the 76 counties in which 50% or more of the population was served by the sampled water. To calculate the correlation coefficients, the data were weighted by the square root of the sex-specific person-years at risk in the population served by the sampled water supply as estimated by the product of percent of population served and population at risk. The statistical techniques used by the authors, particularly the weighting factors, are not standard and probably tend to decrease statistical significance.

The results of Cantor's analysis are shown in Tables 1 and 2. Among males, a significant ($P \leq 10\%$) positive correlation for the 76 counties was found between nonchloroform trihalomethane (NCTHM) concentration and bladder cancer. When the percent of county population served by the sampled water supply is increased to reduce the misclassification of exposure, correlations with bladder and brain cancer tend to increase. Among women, positive correlations were found between total THM's and lung cancer and between NCTHM and bladder cancer. The lung cancer

correlation coefficients did not show a dose-response relationship with the proportion of the population receiving the measured water. But the correlations with bladder cancer did; from 85% to 100% reached conventional significant (P=0.02). A preliminary analysis showed a fairly strong association between halomethane levels and colon cancer rates, but control for composition of the population by ethnicity removed this association.

The authors computed correlation coefficients separately for three geographic regions (North, South, and Mountain Pacific) for the 51 counties in which 65% or more of the population received measured water. There were positive correlations between NCTHM and bladder cancer in males in all regions combined (r=0.30, P=0.03) and in females in each region separately as well as combined (combined r=0.33, P=0.02). For men in the North, a significant correlation was observed between NCTHM and bladder cancer (r=0.52, P=0.02).

Hogan et al. conducted a similar study, in which they related earlier cancer mortality data to chloroform levels in finished water as determined by the same surveys. They used the National Cancer Institute's 20-year age-adjusted county cancer mortality rates for white men and women (Mason et al. 1974) and county chloroform concentrations in drinking water estimated from the EPA's NCRS and Region V surveys (U.S. Environmental Protection Agency 1975). Regression equations were fitted to the mortality rates,

using as independent variables chloroform concentrations, 1960 county population, county population density, percent of county that is urban, percent of county population that is nonwhite, percent of county population that is foreign born, median number of school years completed by county residents over age 25, median family income of county, and percent of county work force engaged in manufacturing. Weighting was by total population exposed (both sexes and all races combined).

The results for sites where any association approached statistical significance are shown in Table 3. The data are consistent with an increase in cancer rates of the rectum, the bladder, and possibly the large intestine with increased chloroform concentration.

McCabe showed that age-adjusted total cancer mortality rates correlated positively with estimated chloroform concentrations in 80 cities. Since no allowance appears to have been made for any of the confounding factors, it is inappropriate to draw conclusions from this study to compare with the Cantor and Hogan studies.

All studies were seriously limited by the absence of data on past exposures, which are the only ones that are directly relevant to cancer that has already been diagnosed. Similarly, all studies were deficient in identifying populations that were stable in the areas where the water quality was studied.

None of these papers discuss the nature of the correlation or regression coefficients obtained. In particular whether the positive results found were due to one or two extreme observations or to a more relevant trend over the range of THM values. Similarly none discussed the adequacy of using a simple linear regression equation to allow for certain confounding variables. Without such discussion interpretation must be especially circumspect.

Results of these studies demonstrate the problems of establishing relationships between health statistics and environmental variables, and lend emphasis to the caution with which they should be interpreted.

Prospects for Further Epidemiological Study

Adequate exploratory and hypothesis-generating work has been done. Studies raising suspicion of higher cancer rates among persons whose major water supplies came from surface waters with generally higher THM concentrations compared to rates among those whose major water sources were ground waters have been followed by attempts to relate the cancer rates to actual THM concentrations. Further studies of this kind are unlikely to lead to more useful information, although an examination of age-specific data might prove fruitful. Consequently, future studies should be more specific and should examine possible confounding factors in detail.

When developing actual exposure data, i.e., THM concentrations in water consumed, investigators should gather information concerning duration of exposure to a particular water source. Further investigation of the validity and reliability of chemical analyses of water constituents would also be in order. Such epidemiological studies without experimental intervention usually cannot uncover small effects. Moreover, with so many confounding factors, it would be difficult to ascribe an effect to any factor with certainty.

Designs for further studies may be conveniently divided into two major types for discussion: case-control studies and cohort studies, including intervention studies.

Case-Control Studies

These studies can start with cases (incidence, prevalence) or deaths. For certain investigations the information from deaths may be adequate. However, the degree of detail necessary for investigating carcinogens in water makes it highly desirable that information be collected from the subjects themselves, rather than from near relatives or other proxies. Some populations are exposed to varying amounts of chloroform, e.g., users of certain cough medicines and toothpastes that contain high concentrations of chloroform. Such individuals should be identified among cases and controls.

The site most warranting a case-control study is the bladder, possibly followed by the colon and rectum. Confounding factors include occupation, cigarette smoking, use of alcohol and other drugs (including artificial sweeteners), nonaqueous sources of THM, coffee consumption, socioeconomic status, and ethnicity.

Cohort Studies

Cohort studies, attempting to follow "exposed" and unexposed populations over time, may also be possible. Some natural experiments have been created by using different methods of water purification. Thus, a population from a community using activated charcoal filtration that is adequately and frequently regenerated might be compared over

time with a population from a community not using that process. Due attention must be given to latency--the time difference between initial exposure and the appearance of disease. This applies to both retrospective and prospective studies.

Studies should be undertaken only after there is a clear understanding of the magnitudes of detectable differences. Because the effects anticipated from the usual concentrations of THM in drinking water are not expected to be large, large populations must be studied to demonstrate associations. Similarly, if there is no association, large populations must be studied to exclude the existence of the small effects that have been postulated.

Some useful data may be available from foreign countries—and the help of international agencies (World Health Organization-International Agency for Research on Cancer, North Atlantic Treaty Organization, U.S.-Japan Scientific Exchange, U.S.-USSR Scientific Exchange) should be sought.

Table 1. Correlation coefficients between residual mortality rates in white males and halomethane levels in drinking water, by percent of the county population served by the sampled supply.[a]

Site or type of malignancy	Halomethane[b] indicator	Correlation coefficients and (P-value for two-tailed t-test) by county population served, %			
		50%-64%, 25 counties	65%-84%, 26 counties	85%-100%, 25 counties	50%-100% 76 counties
Pancreas	Chloroform	0.04 (0.83)	-0.06 (0.77)	-0.32 (0.12)	-0.13 (0.27)
Prostate	Chloroform	0.34 (0.10)	0.03 (0.87)	0.30 (0.14)	0.17 (0.14)
Bladder	NCTHM	-0.22 (0.29)	0.29 (0.15)	0.38 (0.06)	0.19 (0.10)
Kidney	Chloroform	-0.16 (0.44)	-0.11 (0.60)	0.42 (0.04)	0.07 (0.55)
Brain	NCTHM	0.10 (0.65)	0.18 (0.37)	0.24 (0.25)	0.17 (0.14)
Non-Hodgkin's lymphoma	NCTHM	-0.33 (0.11)	-0.19 (0.36)	0.36 (0.08)	-0.03 (0.81)
Stomach[c]	Total THM	0.01 (0.96)	0.05 (0.81)	-0.14 (0.49)	-0.02 (0.87)
Pancreas[c]	NCTHM	-0.12 (0.57)	-0.31 (0.12)	0.04 (0.84)	-0.16 (0.18)
Lung[c]	Total THM	-0.02 (0.94)	0.02 (0.90)	0.15 (0.46)	0.07 (0.56)

[a] From Cantor et al., 1977.

[b] Abbreviations: NCTHM, nonchloroform trihalomethanes; THM, trihalomethanes.

[c] Included for comparison with results for females, where stronger associations with the listed indicator were observed.

Table 2. Correlation coefficients between residual mortality rates in white females and halomethane levels in drinking water, by percent of the county population served by the sampled supply.[a]

Site of type of malignancy	Halomethane[b] Indicator	Correlation coefficients and (P-value for two-tailed t-test) by county population served, %			
		50%-64%, 25 counties	65%-84%, 26 counties	85%-100%, 25 counties	50%-100%, 76 counties
Stomach	Total THM	0.01 (0.97)	-0.11 (0.59)	-0.36 (0.07)	-0.16 (0.17)
Pancreas	NCTHM	-0.31 (0.13)	-0.12 (0.56)	0.31 (0.14)	-0.03 (0.82)
Lung	Total THM	0.25 (0.23)	0.28 (0.17)	0.15 (0.46)	0.22 (0.05)
Bladder	NCTHM	-0.01 (0.97)	0.21 (0.30)	0.45 (0.02)	0.21 (0.06)
Pancreas[c]	Chloroform	-0.25 (0.22)	0.20 (0.32)	-0.06 (0.77)	0.02 (0.85)
Kidney[c]	Chloroform	-0.33 (0.11)	0.19 (0.37)	-0.04 (0.83)	-0.01 (0.96)
Brain[c]	NCTHM	-0.07 (0.73)	-0.03 (0.90)	0.19 (0.35)	0.04 (0.72)
Non-Hodgkin's lymphoma[c]	NCTHM	-0.36 (0.08)	0.26 (0.20)	-0.04 (0.83)	0.01 (0.97)

[a] From Cantor et al., 1977.

[b] Abbreviations: THM, trihalomethanes; NCTHM, nonchloroform trihalomethanes.

[c] Included for comparison with results in males, where stronger associations with with the listed indicator were observed.

Table 3. Weighted regression coefficients and levels of statistical significance between chloroform concentrations and cancer mortality in men and women.[a]

	White males				White females			
	NORS		Region V		NORS		Region V	
ite	β	P	β	P	β	P	β	P
irge Intestine	.0114	0.01	.0115	0.01	.0102	0.01	-.0019	0.6
:ctum	.0032	0.22	.0062	0.03	.0031	0.04	.0007	0.3
.adder	.0034	0.10	.0013	0.63	.0017	0.04	.0023	0.0
.ver	-.0026	0.08	.0048	0.03	-.0020	0.21	.0027	0.1
:omach	-.0096	0.04	-.0023	0.65	-.0069	0.01	.0016	0.6
ophagus	-.0040	0.06	.0016	0.53	-.0005	0.35	.0003	0.6
ngue	-.0045	0.12	.0052	0.02	-.0001	0.80	.0000+	0.9

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